Kaohsiung Journal of Medical Sciences (2014) 30, 248–253

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ORIGINAL ARTICLE

Dose-dependent attenuation of intravenous nalbuphine on epidural morphine-induced pruritus and analgesia after cesarean delivery

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Received 25 March 2013; accepted 17 October 2013
Available online 18 February 2014

KEYWORDS
Cesarean delivery;
Epidural morphine;
Nalbuphine;
Patient-controlled antipruritus

Abstract Epidural morphine in patient-controlled analgesia regimens controls postoperative pain well but easily induces pruritus and other epidural morphine-related side effects. With 90 pregnant American Society of Anesthesiologists physical status II females scheduled for elective cesarean delivery, the present study was designed to evaluate the efficacy and safety profile of patient-controlled antipruritus (PCP) use of intravenous nalbuphine-based regimens for attenuation of postoperative pruritus and related side effects in combination with epidural morphine patient-controlled analgesia with regard to the quality of postoperative pain management. Patients were randomly assigned to two nalbuphine groups (5 μg/kg/hour, Group N5 or 10 μg/kg/hour, Group N10) and bolus dose of 1.6 μg/kg for PCP or the control (normal saline) group. Comparable visual analog scale scores for rest pain at each measured time interval among the three groups demonstrated that adequate pain relief was offered; however, the cumulative dose of nalbuphine administered to the patients in Group N10 attenuated the analgesic effect of epidural morphine in moving pain at POh24 only. Fewer episodes and milder severity of pruritus were observed in patients in Groups N5 and N10 at all postoperative time intervals. Epidural morphine provided good postoperative pain relief but with incommodious

Conflicts of interest: All authors declare no conflicts of interest.

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http://dx.doi.org/10.1016/j.kjms.2014.01.001

side effects. In addition, intravenous nalbuphine not only attenuated the incidence of pruritus but also decreased total morphine consumption. In conclusion, intravenous administration of low-dose nalbuphine (5 μg/kg/hour) for PCP maintained analgesia produced by epidural morphine and offered low pruritus incidence.

Introduction

Cesarean delivery is one of the most common surgical procedures, performed at an increasingly high rate [1]. A patient-controlled administration device to deliver analgesic agents is frequently used for postoperative pain management for patients undergoing cesarean delivery, because opioid-based regimens are the "gold standard" of cesarean delivery analgesia [1]. The epidural morphine setting for patient-controlled analgesia (PCA) provides good postoperative pain relief; however, opioid-related side effects, for example, nausea, vomiting, and pruritus, discourage patients from attempting the use of PCA [2–5]. Reduction of epidural morphine-related side effects during PCA use thus becomes a major issue to improve quality.

A combination of various adjuvant agents with morphine in the PCA regimen reduces the dose of morphine and therefore decreases the incidence and severity of morphine-related side effects. Nalbuphine is a mixed kappa opioid agonist and mu opioid antagonist which possesses and restores the analgesic properties of morphine while inhibiting the action of morphine on mu opioid receptor-induced side effects at the same time when it is coadministered with morphine [6–9]. In addition, nalbuphine is superior to naloxone for the treatment of side effects after epidural morphine administration [10]. It therefore appears to be a potential candidate for combination in postoperative pain control regimens. However, the duration of epidural morphine-induced pruritus may extend over the effect of single nalbuphine dosage and it is difficult for pruritus after surgical pain has faded. Whether low-dose nalbuphine intravenous delivery to patients provides an antipruritic effect but without a decreased analgesic effect has not been determined. The present study was designed to evaluate the efficacy and safety profile of patient-controlled antipruritus (PCP) use of nalbuphine-based regimens in combination with epidural morphine PCA with regard to the quality of postoperative pain management for adult patients who underwent cesarean delivery.

Materials and methods

In total, 90 pregnant American Society of Anesthesiologists physical status II females who were scheduled for elective cesarean delivery were screened for enrollment in this prospective, randomized, single-blind study after institutional approval was obtained. Patients were excluded if they had a history of chronic opioid use, dermatitis, itchy skin, or fit in absolute or relative contraindication to neuraxial anesthesia. Eligible patients were then randomly assigned, through a computer-generated random number list concealed in an opaque envelope, to the two nalbuphine groups or to the control group after written informed consent was obtained.

Participants were offered 12–15 mL of 2% lidocaine with epinephrine 5 μg/mL and fentanyl 100 μg for lumbar epidural anesthesia. Intravenous midazolam (0.03 mg/kg) was allowed for adjuvant medication if patients felt anxious before baby delivery. After delivery, a loading dose of 10 mL of epidural morphine (0.06 mg/mL) with bupivacaine (1 mg/mL) was administered by a PCA device and analgesia was maintained at an infusion rate of 3 mL/hour with a bolus dose of 1 mL and a 20-minute lockout for 36 hours according to the study protocol. In nalbuphine groups, patients either received intravenous nalbuphine 5 μg/kg/hour (Group N5) or 10 μg/kg/hour (Group N10) by another patient-controlled device for antipruritus with a setting of bolus dose of 1.6 μg/kg and a 10-minute lockout for 48 hours. In the control group (Group C, $n = 30$), normal saline was offered instead.

The primary outcome was pain (at rest and moving, such as changing body position) assessment at 12 hours, 24 hours, 36 hours, and 48 hours (POh12, POh24, POh36, and POh48) postoperatively using the visual analog scale (VAS) for pain in which 0 is defined as no pain and 10 as maximum pain. The following variables were defined as secondary outcomes: incidence of postoperative nausea and vomiting, and antiemetic therapy requirements; incidence of pruritus (patients were specifically asked about the desire to scratch); and incidence of urinary retention (defined as the requirement of bladder recatheterization after 24 hours postoperatively). These variables were also assessed at 12 hours, 24 hours, 36 hours, and 48 hours postoperatively through a standardized questionnaire administered by interview by the study team member blinded to the patient group assignment. Data were later crosschecked with data from nursing staff records. Intravenous naloxone (0.1 mg) was used in the ward as a rescue for pruritus if requested. Intravenous pethidine (0.25 mg/kg) was offered for inadequate resting pain relief (VAS score ≥ 6).

Statistical analyses for the study were performed using SPSS 12.0 for Windows (SPSS Inc., Chicago, IL, USA). *A priori* sample size analysis determined a sample size of at least 22 patients per group to have a probability of 80% chance suffering from pruritus in the control group and a 50% decrease of incidence to 40% pruritus in the experimental groups with a power of 0.8 and $\alpha =$ of 0.05, and the authors selected 30 patients per group for unexpected bias. Descriptive statistics were applied on every variable. Demographic and clinical data were analyzed using one-way analysis of variance and post-hoc test with Bonferroni corrections. A p-value <0.05 was considered statistically significant.

Table 1 Demographic data of the study population.

	Group C	Group N5	Group N10
Patients, *n*	30	30	30
Age, y[a]	31 (23–39)	30 (25–38)	29 (25–38)
Body mass index	28.3 (3.5)	27.0 (4.7)	27.5 (4.0)

[a] Data are medium (range).

Results

The preliminary results of the study revealed no significant difference among the groups in terms of demographic characteristics, which included age and body mass index (Table 1). Three patients in Group C suffered from severe pruritus induced by epidural morphine at POh24 even after intravenous antihistamine was offered. Naloxone was therefore given to these patients for the relief of generalized itching and they were thereby excluded from the study at POh24. Nalbuphine intravenous intake at each time interval is shown (Fig. 1). Total intake of nalbuphine in Group C, Group N5, and Group N10 was 0 mg, 16.1 ± 2.8 mg, and 30.0 ± 4.4 mg, respectively. Total intake of morphine in Group C, Group N5, and Group N10 was 3.9 ± 0.5 mg, 3.4 ± 0.5 mg, and 3.3 ± 0.6 mg, respectively (Fig. 1, Group C vs. Group N5, $p = 0.001$; Group C vs. Group N10, $p < 0.001$).

The study showed comparable VAS scores for both resting pain and moving pain at POh12, POh36, and POh48 among the groups, demonstrating that adequate pain relief was offered (Fig. 2A and B). No patient needed pethidine administration to relieve resting or moving pain.

Both fewer episodes and milder severity of pruritus were observed for patients in Groups N5 and N10 at all

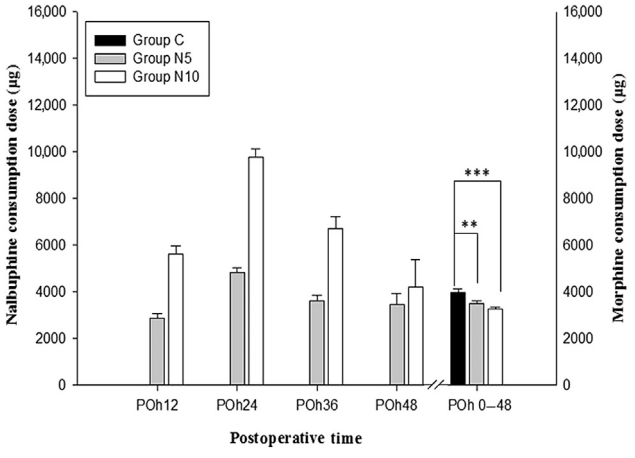

Figure 1. Intake of intravenous nalbuphine and epidural morphine doses. Doses of intravenous nalbuphine with bolus and infusion are presented at each time interval. There is a significant difference in Group C compared with Groups N5 or N10. Doses of epidural morphine are presented as total dose intake. There was a significant difference among groups. Group C: without nalbuphine administration; Group N5: intravenous nalbuphine, 5 μg/kg/hour; Group N10: intravenous nalbuphine, 10 μg/kg/hour.

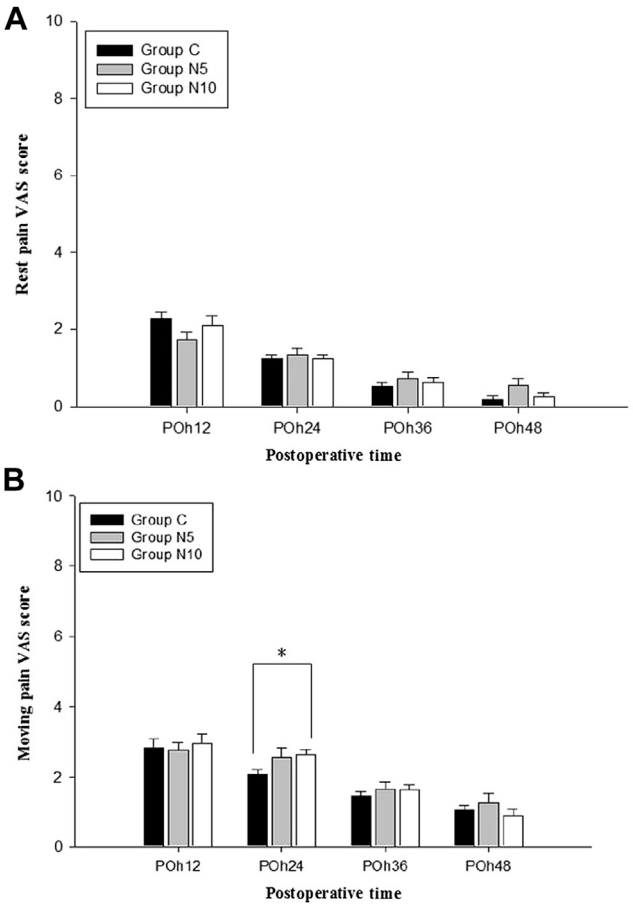

Figure 2. Scores of postoperative resting and moving pain measured by visual analog scale (VAS). (A) In resting pain, comparable pain scores among the three groups are shown at each time interval. (B) In moving pain, Group N10 showed high scores compared with Group C (*$p = 0.026$, one-way analysis of variance) at POh24. Comparable pain scores obtained at the other time intervals among the three groups. Group C: without nalbuphine administration; Group N5: intravenous nalbuphine, 5 μg/kg/hour; Group N10: intravenous nalbuphine, 10 μg/kg/hour.

postoperative time intervals. In addition, the severity of pruritus induced by dressing tape was significantly milder for patients in Groups N5 and N10 at POh48 (Group C vs. Groups N5 and N10, $p = 0.021$; Table 2). Among the patients in Group C, there were 17 out of 30, 22 out of 30, 17 out of 27, and 10 out of 27 patients who suffered from pruritus at POh12, POh24, POh36, and POh48, respectively (Tables 2 and 3). Therefore, the overall incidence of pruritus during epidural morphine PCA ranged between 37% and 73% (morphine was offered for 36 hours postoperatively).

Other side effects recorded for the study included nausea (Group C = 3/30; Group N5 = 0/30; Group N10 = 2/30), vomiting (Group C = 2/30; Group N5 = 0/30; Group N10 = 1/30), and headache (Group C = 2/30; Group N5 = 0/30; Group N10 = 1/30), which demonstrated comparable incidences without significant differences among the groups. No dizziness was noted for patients in Group C regardless of whether the patients were in resting,

Table 2 Pruritus locations caused by epidural morphine with or without intravenous nalbuphine administration.

Time	Location	Group			*p*
		C[a]	N5	N10	
POh12	Face and neck	6	5	2	0.118
	Limbs	4	2	7	
	Trunk	8	5	1	
	Back	5	5	2	
	Patients suffered	17	10	8	
	Did not suffer	13	20	22	0.044*
POh24	Face and neck	10	5	5	0.573
	Limbs	16	2	9	
	Trunk	16	5	4	
	Back	12	5	3	
	Patients suffered	22	12	12	0.005**
	Did not suffer	8	18	18	
POh36	Face and neck	8	2	2	0.99
	Limbs	11	4	5	
	Trunk	10	3	3	
	Back	9	3	2	
	Patients suffered	17	9	8	0.009**
	Did not suffer	10	21	22	
POh48	Face and neck	2	0	**0**	0.661
	Limbs	7	0	**0**	
	Trunk	6	1	**1**	
	Back	5	1	**2**	
	Patients suffered	10	2	**1**	0.001**
	Did not suffer	17	28	**29**	
Dressing tape on back Pruritus					
Yes		16	7	9	0.021*
No		11	23	21	

*$p < 0.05$.
**$p < 0.01$.
[a] Thirty patients collected in Group C in POh12 and POh24 time intervals and 27 patients collected in POh36 and POh48 time intervals.

Table 3 Intravenous nalbuphine attenuates the incidence and severity of pruritus induced by epidural morphine.

Time	Grade	Group			*p*
		C	N5	N10	
POh12	None	13	18	22	0.043*
	Mild	16	12	8	
	Moderate	1	0	0	
	Severe	0	0	0	
POh24	None	8	15	17	0.016*
	Mild	16	15	13	
	Moderate	3	0	0	
	Severe[a]	3	0	0	
POh36	None	10	21	21	0.036*
	Mild	14	8	9	
	Moderate	3	1	0	
	Severe	0	0	0	
POh48	None	16	28	29	<0.001***
	Mild	11	2	1	
	Moderate	0	0	0	
	Severe	0	0	0	

*$p < 0.05$.
***$p < 0.001$.
[a] Three patients in Group C were categorized to severe grade because pruritus needed naloxone infusion.

sitting, or standing positions. However, three patients in Group N10 showed mild dizziness at POh12 ($p = 0.035$, Group N10 vs. Groups C and N5), and symptoms then subsided without further treatment. No patient complained of backache during the study.

Discussion

In the present study, epidural morphine PCA provided adequate postoperative pain control in post-cesarean delivery patients but with up to 22 out of 30 (73%) patients suffering from pruritus. Epidural morphine combined with low-dose intravenous nalbuphine for PCP still provided adequate postoperative pain control. However, reversal of analgesic effect of epidural morphine was found in patients in Group N10 for presentation of high VAS score in both categories of resting or moving pain.

Epidural morphine for postoperative pain control was associated with side effects of nausea and vomiting, pruritus, urinary retention, and gastrointestinal ileus [11–13]. The incidence of pruritus for parturients after cesarean delivery using spinal morphine was >70% [4,8,14,15]. The high overall incidence of itching discouraged patients from the use of epidural morphine [2,3], because surgical manipulation may contribute to gastrointestinal ileus and urinary retention [3], and fluid management may influence the incidence of nausea and vomiting [13]. Accordingly, the authors focused on pruritus attenuation for nalbuphine PCP use and attempted to improve both the quality and acceptance of postoperative analgesia after cesarean delivery. Although the analgesic duration was not correlated with the dosage in a range of 2–5 mg of epidural morphine [16], the more intraspinal morphine administered the higher the pruritus incidence [17]. Nalbuphine has been demonstrated to decrease neuraxial morphine-induced pruritus either via bolus or infusion administration [8,16,18]. However, proper dosage for intravenous nalbuphine for patients to receive epidural morphine for good analgesia without the side effect of pruritus is not yet determined. A combination of intravenous low-dose nalbuphine (10 μg/mL) and morphine (1 mg/mL) showed no effect in decreasing pruritus incidence [19]. Penning et al. [20] demonstrated that 0.1 mg/kg of intravenous nalbuphine was needed to antagonize pruritus for patients who received 0.1 mg/kg of epidural morphine for analgesia for elective total abdominal hysterectomy [20]. However, another study revealed that intravenous infusion of nalbuphine at 60 μg/kg/hour decreased pruritus in total hysterectomy patients receiving an epidural of 3 mg of morphine for postoperative pain management [7]. In the present study, intravenous low dose of nalbuphine (5 μg/kg/hour) was demonstrated to decrease the incidence and severity of pruritus caused by epidural morphine. We believe that this is attributed to the significantly reduced morphine doses used in the study groups. In other words, intravenous

nalbuphine tapers the dose of epidural morphine. Similar results were evidenced by Yeh et al. [21], demonstrating that optimal combination of morphine and nalbuphine in PCA decreases the incidence of pruritus in a ratio-dependent manner. Whether other ultra-low doses of nalbuphine show similar effects to attenuate side effects is not realized. Further investigation should be carried out to elucidate the optimal nalbuphine dose for epidural morphine-induced pruritus.

Different drugs are used to prevent or to treat postoperative pruritus, which include antihistamines (e.g., diphenhydramine, promethazine), 5-HT3 (serotonin) receptor antagonists (e.g., ondansetron, droperidol), opioid antagonists (e.g., naloxone, nalmefene), opioid agonist antagonists (e.g., nalbuphine), and nonsteroidal anti-inflammatory drugs [22—24]. Morphine is believed to lead to histamine release and increase serum histamine [25]. However, when neuraxial morphine is used, pruritus does not seem to be attributed to histamine release solely. Antihistamines such as promethazine have been reported to be effective for pruritus [26]; nevertheless, antihistamines for prevention of epidural morphine-induced pruritus are still contradictory as well as/unlike serotonin receptor antagonists [8,27,28]. In surgical patients, various doses of naloxone were used mainly for the reversal of epidural morphine-induced respiratory depression; in addition, a tendency for dose-related decreases in pruritus and nausea was noted. However, higher naloxone dose adversely affected analgesia [10,25,29]. In the current study, the authors found no change in analgesia after a low dose of nalbuphine (Group N5) was offered, whereas moving pain scores increased significantly at POh24 after a high dose of nalbuphine (Group N10) was offered. In addition, the severity of pruritus induced by dressing tape was significantly milder for patients in Groups N5 and N10 at POh48, indicating that nalbuphine attenuates itching of different origins. Our finding that nalbuphine decreased both incidence and severity of pruritus during the entire 48-hour study period appears to contradict many previous studies in demonstrating an effect.

Our study had some limitations. First, intravenous nalbuphine of 5 μg/kg/hour was defined as "low dose" in the study. A lower dose of nalbuphine to demonstrate similar antipruritus effects without compromising analgesia warrants further study at a larger scale. Second, two patient-controlled devices were needed in the study, which indicated a higher workload for nursing staff. However, tags on lines and devices were able to clearly register each line function and prevent improper treatment in the present study. Third, the study was designed for the reduction of opioid-related side effects during epidural morphine PCA. A large, prospective randomized study is warranted to determine whether the study results can be extrapolated to other neuraxial anesthesia.

In conclusion, epidural morphine PCA provides good postoperative pain relief but with incommodious side effects for patients undergoing cesarean delivery. In the present study, intravenous low-dose nalbuphine (5 μg/kg/hour) for PCP maintained analgesia produced by epidural morphine and offered low pruritus incidence. Low-dose nalbuphine with intraspinal morphine should be recommended in patients undergoing cesarean delivery because it is efficacious to attenuate morphine-induced pruritus without compromising postoperative analgesic effects.

Acknowledgments

The study was approved by the Institutional Review Board of Kaohsiung Medical University Hospital (KMUH-IRB-96032). The authors thank Mr Richard H. Davis, MA, English as a second language teacher for his gratuitous assistance of English grammar examination and editing. The authors also thank Yu-Tung Feng, MS, Pharmacy, for his assistance in collecting data, making preliminary analyses, and putting together the draft.

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